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October 7, 2003

Dr. Mark McClellan
Commissioner
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Re: Docket No. 2003P-0274/CP1 – Response to submission from Ms. Musa Mayer *et al.* regarding "Tier 1 Initial Approval"

Dear Commissioner McClellan:

The Abigail Alliance for Better Access to Developmental Drugs recently learned that you have received a letter dated September 15, 2003, opposing our June 2003 petition for adoption of our Tier 1 Initial Approval concept to improve access to investigational therapies for patients with no approved treatment options. We would like to respond to the main assertions in that letter (hereinafter the "Mayer letter").

Background

The Abigail Alliance is made up almost entirely of cancer patients, survivors, caregivers, and family members of patients who are still fighting or who have lost their courageous battles with deadly diseases. Our president, Frank Burroughs, is the father of Abigail Burroughs who died at the age of 21 after having been denied access to several investigational drugs that might well have helped her. The Tier 1 Initial Approval concept was written by the Abigail Alliance Advisor on FDA and Regulatory Issues, Steven Walker, who recently lost his wife to colon cancer at the age of 47. Our counsel in these actions is the Washington Legal Foundation, a public interest law and policy center based in Washington, D.C.

The Tier 1 Initial Approval concept, the petition to the FDA, and our lawsuit have all grown out of our personal experiences with the flaws in our system, and our more than two years of intensive efforts trying to bring this issue to the fore on behalf of our members and constituents. Additional information regarding the Abigail Alliance, our

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inception, activities, mission and goals, our Tier 1 Initial Approval concept, our petition to the FDA, and the lawsuit can be found on our website at *www.abigail-alliance.org.*

It may be of interest to you that the Abigail Alliance actively sought input on the Tier I concept from several patient advocacy groups prior to submitting the initial and revised versions of the document to the FDA. In both cases we received almost universally positive reactions from those that responded to our request for comments. Upon receipt of the March 5, 2003, Tier 1 Initial Approval concept document, the FDA contacted us to schedule a meeting with a Senior Associate Commissioner to further discuss the idea. We later presented the concept to you at a meeting attended by representatives of several patient advocacy groups, receiving only positive feedback. The concept was introduced to the FDA, advocates, industry and others at the March 12, 2003, Oncologic Drugs Advisory Committee (ODAC) meeting regarding Accelerated Approval, and has been extensively reported in the trade and lay press. We offer this partial summary of our efforts to publicize our activities as evidence that we are trying to educate people regarding the problem, elevate the issue, encourage debate, and find solutions. Our petition and the lawsuit are the most recent manifestations of that effort.

It is important to note that the Mayer letter does not purport to represent a consensus of opinion among patient advocates. Indeed, it was signed by no more than half of the FDA and ODAC patient advocates/representatives to whom Ms. Mayer circulated it (who, in turn, do not necessarily reflect the views of the broader patient advocacy community on all issues).

The Objections in the Mayer Letter Are Not Proper Grounds For Rejecting Tier 1 Initial Approval

We have organized our input to you by reprinting excerpts from the Mayer letter followed by our position or responses on the issues raised in the excerpts.

Excerpt No. 1

We are writing to you today in response to the Abigail Alliance citizen petition and recent lawsuit concerning the so-called "Tier 1" approval initiative, a proposed mechanism for permitting the marketing of drugs after Phase I testing to terminally ill patients who have exhausted other treatment options and are ineligible for clinical trials.

We want you to know that advocates don't speak with one voice, and that we strongly feel that this Tier 1 initiative is misguided and is likely to cause more harm to patients and to the entire drug development program.

Response

The job of patient representatives is to bring the patient perspective to the ODAC's deliberations and ask the tough questions on their behalf. Patients frequently do not agree with the positions taken by the FDA, the ODAC, researchers and others with perspectives different from those of patients. Unfortunately, the Mayer letter takes numerous positions that are counter to the views of thousands of intelligent and informed patients, many of whom suffer from the most deadly forms of cancer and other diseases who are searching for and are routinely denied access to treatment options with potential to improve, extend and even save their lives. They are supporting us because the problems they encounter are the very problems the Abigail Alliance is working to fix.

We note with dismay that the Mayer letter is signed by twelve individuals in their capacities as FDA or ODAC patient advocates/representatives. These positions of responsibility are intended to facilitate input to the FDA and ODAC from patients and patient groups, not to serve as a vehicle for opposing it. While we acknowledge the right of all parties to comment on our efforts and ideas in their *individual* capacities, we question the propriety of patient representatives to ODAC, or patient consultants to the FDA, using those positions of responsibility to organize or participate in efforts to fight the initiatives of legitimate, responsible, and widely-supported patient groups. This is especially true where, as here, the advocates/representatives have declined to engage in meaningful dialogue with those they have chosen to oppose.

We feel it is important for patient advocates charged with the responsibility of advising the FDA on the patient's perspective to listen carefully to patients, and to try to bring the views of those patients into the system – especially patients suffering from life-threatening diseases with unmet needs who are finding themselves abandoned to die by the current system.

Excerpt No. 2

As you know, the claim that drugs have already demonstrated sufficient safety and efficacy after Phase I trials is untrue. Phase I trials are small dose-finding/safety studies, usually with fewer than fifty patients, often with a number of different kinds of cancer. What may appear to be a positive response in a handful of patients in a Phase I study must be further explored with at least a hundred or more patients in a Phase II trial, and then confirmed in much larger Phase III studies (typically thousands of patients) that are randomized, controlled and ideally blinded. A Phase I study might well involve only a few patients exposed at the intended dose. In such cases, it is quite possible that there might be a high incidence of serious and even fatal acute adverse events associated with a new drug, without this being observed, due to chance. If as the Abigail Alliance urges, drugs are given "early conditional approval" following Phase I trials, drug interactions, dose

optimization, subacute toxicity, and many other aspects of safety assessment will not be completed before these patients have access to the drugs.

Response

We agree that new drugs are far from fully evaluated at the end of a Phase I trial. It is also true, however, that some patients with no other treatment options who are facing certain death in the near-term from their disease will – in consultation with their physicians – properly view the risk of trying the new drug in a Phase II trial as a reasonable and even desirable thing to do.

For every patient who manages to enroll in the Phase II trial, there are others who are denied entry because of their disease condition, prior treatment history, limited space in the trial, and numerous other factors. Aside from the fact that they simply aren't in the right place at the right time with the right disease conditions and prior treatment history, they are identical in the risk they face as the patients who get into the trial. Some were probably even encouraged by the FDA, NCI and advocacy groups to try to get into a trial. Most will not qualify, and many others for various reasons will fail to gain entry to the trials they pursue, and will be denied a chance to extend and even save their lives through no fault of their own. They end up dying prematurely as victims of both their disease and a system that is not designed to respond to their needs.

In fact, the statement that drugs don't show evidence of safety and effectiveness in Phase I trials is becoming increasingly untrue. It is an old dogma that grew out of the frequent failures of cancer drug research when we knew little about the causes of the diseases and the mechanism(s) of action of the new drugs we were testing. Our rapidly advancing knowledge of the root causes of disease, and our expanding ability to make drugs that specifically target the root causes without causing severe side effects, is making early evidence of safety and effectiveness an increasingly more frequent occurrence. We are emerging from Edison style drug discovery (try thousand of compounds in the lab to find ten for animal testing and one for human testing) into knowledge-based drug invention (identify the disease mechanism then invent a drug to block it).

Excerpt No. 3

While we too are deeply saddened that some patients die awaiting drug approval, we strongly believe that the clinical trials system is the only method we currently have of achieving reasonable certainty that new drugs are safe and effective. We believe that the existing mechanisms of Single Patient IND's for compassionate use, expanded access programs, and accelerated approval, while not perfect solutions, are reasonable and good-faith efforts to get drugs to the patients who need them most desperately at the earliest time that is reasonable.

Response

The language in this comment that "some patients die awaiting drug approval" is a very significant understatement of the problem. The "some" is actually hundreds of thousands of Americans every year, a catastrophe of immense proportions. The Abigail Alliance and its members consider this increasingly preventable loss of life from disease to be among the direst emergencies we face in the United States. Unfortunately, our system includes no true "emergency response" mechanisms. Tier 1 would provide such a mechanism.

The belief that "the existing mechanisms . . . are reasonable and good-faith efforts to get drugs to patients who need them most desperately at the earliest time that is reasonable" is belied by the track record of those mechanisms. It is obvious that our current mechanisms have fallen far short of meeting the legitimate need for access. Basing policy on the assumption that the current mechanisms cannot be improved upon guarantees that we will continue to fail. Of the hundreds of thousands of patients who would avail themselves of access if it were available, only a small fraction actually gain access within the current system.

The problem is not a question of medical ethics. The FDA will now allow access to patients if their physician requests it and the sponsors agree to provide the drug, but the system is simply unworkable because it fails to deal with the economic realities involved in manufacturing, distributing, and treating tens of thousands of patients with a drug essentially for free. The FDA also will approve large Treatment INDs (expanded access programs), but few companies offer them, and those that do usually offer programs that are far too small, meeting only a fraction of the need.

Excerpt No. 4

Clearly in addition to the danger to patients posed by the Abigail Alliance proposal, making drugs available to the public prior to full approval can have extremely negative effects on the completion of clinical trials.

It was evident at the last meeting of the Oncologic Drugs Advisory Committee, in March, 2003, that when an investigational drug becomes available in the marketplace, there is a clear negative effect on trial enrollment for the post-marketing mandated Phase III randomized trials required under Accelerated Approval regulations. We believe that these mandated confirmatory trials simply must be done, unless we're prepared to have potentially toxic, expensive and ineffective drugs on the market, with little control or guidance.

Response

Protection of clinical trials is addressed in Tier 1 Initial Approval. Only patients who have been denied access to a clinical trial, or that are considered poor candidates for a clinical trial, will be allowed to obtain Tier 1 drugs through their physician. Contrary to the implied position of the Mayer letter, patients often cannot wait to find out if they will qualify for a clinical trial. In fact, gaining entry to a clinical trial is an extremely uncertain and risky pursuit for cancer patients, sometimes resulting in declining health for some patients because they must forego treatment for four to six weeks as a condition of eligibility, and then meet all the other usually very restrictive entry criteria at the time of actual enrollment. Thousands of patients are dying who could not possibly qualify for a clinical trial, in any case, by virtue of their age or because their disease profile does not fit trial protocols.

Please be aware that Mr. Walker of the Abigail Alliance spoke at the March 2003 ODAC meeting and pointed out that the primary reason for poor performance in completing Phase IV (not Phase III as stated in the excerpt) clinical trials is an insistence by the FDA that the sponsors design trials that cannot be reasonably completed after a drug is approved. The slides from Mr. Walker's presentation are available on our web site.

Excerpt No. 5

Unfortunately, the Abigail Alliance Tier 1 initiative slides precipitously down the same slippery slope away from evidence-based medicine. If unproven drugs are marketed after Phase I, we believe that this will have the effect of undermining the entire cancer drug development process, as patients scramble to make themselves eligible for access. For patients, the incentive for trial participation would be seriously compromised by permitting them access if "in the judgment of their physician, [they] are not reasonable candidates for a clinical trial," to quote from Abigail Alliance materials. Among the disqualifying "reasonable" factors listed would be the inconvenience of travel, a stipulation that virtually guarantees broad eligibility. Moreover, if these drugs are already being marketed to patients, drug companies would clearly lack incentive to move ahead with the necessary trials that would result in accelerated or full approval. We believe that this initiative will actually slow down the pace of drug development and thereby harm ALL patients who await new drugs, but count on the FDA to ensure their safety and efficacy.

Response

The concept of "evidence-based medicine" is distorted by this argument. In effect, the Mayer letter is arguing that the majority of patients who cannot qualify for a clinical trial, or whose physicians do not believe they can tolerate the washout period, or who lack the energy or funds for long-distance travel, should simply die untreated for the symbolic good of the clinical trials system. This is dangerously backwards thinking.

Tier 1 will alleviate this unacceptable situation for patients and at the same time create an opportunity to entertain more accessible clinical trial designs and more realistic ways of evaluating the trial data. Contrary to the claim in the Mayer letter, Tier 1 will almost certainly result in better clinical trials, faster development programs, and faster approvals.

It also is likely that sponsors will create combination development programs consisting of clinical trials, expanded access programs and Tier 1 approval programs so they can ensure enrollment in the clinical trials they need for accelerated and/or full approval, treat patients with limited financial means or no insurance coverage in the expanded access programs, and use the Tier 1 programs to serve those that either have insurance coverage to cover part or all of the cost of their treatment or that have the means to purchase the drug. Sponsors will do this because it makes sense, it will work, and it will provide them with a model that helps patients, satisfies their investors, offsets development and expanded access costs, and allows them to continue moving their drugs efficiently toward full marketing approval, all at the same time.

In practice, sponsors could set up their programs as follows: a physician would contact the sponsor on behalf of the patient and request the drug, providing the relevant information required for obtaining a drug through Tier 1 approval. The sponsor would then inform the physician of available clinical trials the patient should pursue if he/she is potentially eligible, or direct the doctor to the appropriate expanded access or Tier 1 drug program. Under this approach, the trials would be enrolled as a priority, followed by treating patients outside the clinical trials in expanded access or Tier 1 programs. The primary benefit will be that patients will have greatly expanded access to the drugs they seek when the risk posed by taking the drug is offset by the risk posed by their disease.

It also is critical to note that all of these programs will be occurring under the continuing oversight of the FDA, and will be delivered through our health care system. The drugs will be prescribed and administered by responsible, qualified physicians. Tier 1 does not remove the FDA and other oversight mechanisms from the system, but it does bring in the patients who we are now leaving out.

Excerpt No. 6

Abigail Alliance appears to believe that the profit incentive would offer enough inducement for companies to manufacture these drugs in quantity after Phase 1, to meet patient demand. But how much, realistically, could a manufacturer expect to recoup on this chancy investment in production facilities from the proceeds of such marketing? Such a move might only seem attractive to companies if it permitted them to delay or ultimately even to bypass having to demonstrate drug effectiveness and safety.

Response

This excerpt raises a question of economics. The Abigail Alliance does not believe that sponsors will be driven by the profit incentive, but rather by the removal of disincentives. Tier 1 approval will be a restricted approval, which will carry with it the qualified backing of the FDA that marketing of the drug to a population of patients who fully understand the status of the drug and that have no other treatment options is reasonable and appropriate. Marketing an "approved" drug, no matter how restricted the approval, is more workable than charging recovery costs for an unapproved drug in a Treatment IND or Single-patient IND, which are actually clinical trials.

In summary, charging for a Tier 1 ***approved*** drug is workable; charging for a drug administered in a clinical trial is not. It also is a concept that can be explained to investors as being something potentially beneficial to the company, instead of being viewed as a pure expense for a charitable act that does not carry the tax benefits of a charitable contribution. Receiving Tier 1 approval also will generate considerable interest among investors, further capitalizing the company and allowing it to better fund its development programs. The idea that only companies wanting to bypass demonstrating safety and efficacy in clinical trials would pursue Tier 1 approval is without merit. The restricted marketing allowed by Tier 1 would prevent the sponsor from realizing the full financial potential of the drug, maintaining the incentive to complete the clinical trials and approval process. Further, Tier 1 approval would eventually be withdrawn if the company failed to pursue its development program. Finally, Tier 1 would sometimes provide patients with multiple options for treatment when they run out of approved options and cannot gain entry into a clinical trial, meaning that doctors and patients will most often pursue treatment with drugs from sponsors that are conducting clinical trials and announcing positive results. The concept that companies will be able to successfully "game" the system is just not realistic and in any case can be prevented by withdrawal of the Tier 1 approval.

Excerpt No. 7

In addition, drug companies would be called upon to manufacture the drug in advance of a fully developed manufacturing standard, which would pose major problems with reliability and safety of some drugs. The notion that such products might be broadly used prior to extensive manufacturing review and control followed by inspection programs is problematic, especially during the early development process, when sponsors may not have fully characterized their product or controlled their process. The potential exists for sponsors, either inadvertently or even intentionally, to produce for marketing a drug that differs substantially from that for which safety and efficacy data were submitted to and reviewed by the FDA.

Under the circumstances that this proposal would create, the potential for fraud is high, especially when dealing with people in a desperate quest to save a life.

Response

The point raised in this excerpt is again one of economics, and while it correctly identifies the problem, it draws the wrong conclusion. The problem is one we have now, and also one that Tier 1 will fix. Companies do not gear up to manufacture drugs in quantity now because of the very significant uncertainty regarding the length of time, cost and overall uncertainty built in to our system for obtaining FDA approval of new drugs. These uncertainties apply even to drugs that show exceptional promise early in development. Tier 1 removes some of the financial uncertainty that now keeps companies from building manufacturing facilities early in the drug development process. The cost of building the capacity will be partially or in some cases entirely offset by capital investment resulting from the FDA's Tier 1 approval of the drug, and from the revenues that will be generated by restricted marketing under Tier 1.

The contention that Tier 1 approval would relax manufacturing standards is unfounded. Tier 1 contains no language that would relax manufacturing standards or preclude revision of the existing controls to ensure the quality of drugs manufactured for use under Tier 1. Tier 1 is likely to result in a beneficial effect by creating an incentive for sponsors to plan for increased manufacturing capacity earlier in the process, getting facilities up, running, inspected and approved well before the demand associated with eventual accelerated or full approval is created. Although it is rarely publicly announced, some delays in drug development programs are caused by the need to build and gain approval for manufacturing capacity that is not started until the sponsor is relatively certain that approval is coming in the near term. Early development of capacity would reduce these kinds of delays.

Excerpt No. 8

We strongly believe it is not in the public's interest, and certainly not in the interest of cancer patients, to undermine the clinical trials and regulatory process in this way.

Response

Tier 1 Initial Approval will not undermine the clinical trials system or the regulatory process, nor is it really even a "new" concept. It is a set of incremental and logical changes to better accomplish a goal that Congress, the FDA, and most patient advocates already support. The Food, Drug and Cosmetic Act (FD&C Act) already specifically allows expanded access to unapproved therapies and diagnostics in emergency situations subject to a narrative limitation that "provision of the investigational drug or device will not interfere with the initiation, conduct, or completion of clinical investigations to support marketing approval" (FD&C Act, Section 402). The FDA codified the law in Sections 312 and 314 of the Code of Federal Regulations, but did not include any specific language for protection of clinical trial enrollment.

In contrast, access to a Tier 1 approved drug would be conditioned on specific language in the Code of Federal Regulations as proposed in the following language presented in our petition: "A sponsor receiving Tier 1 Initial Approval must provide the drug only to patients who have been found ineligible for or denied participation in a clinical trial for the same drug or who, in the judgment of their physician, are not reasonable candidates for a clinical trial." This also is not a new or controversial concept as evidenced by the following excerpt from a document distributed by the Marti Nelson Cancer Foundation (MNCF) titled Expanded Access – FAQs (September 2003):

> [Question]: *Some argue that compassionate use gets in the way of clinical trials.*
>
> [Answer]: Exclusion criteria for expanded access can state that if a patient is eligible for the trial, he is ineligible for expanded access.

One of the signatories to the Mayer letter is Ms. Nancy Roach, Director of the MNCF. The MNCF FAQ document (submitted in full with this letter) is a strong justification for allowing EAPS ***and Tier 1***, including the above advice that a provision limiting access to an EAP to patients who aren't eligible for a clinical trial is a valid and effective approach to protect enrollment in clinical trials.

The only provision in the MNCF FAQ document that does not appear to be an argument for Tier 1 is a highly speculative and vague final entry suggesting that allowing a sponsor to profit (presumably instead of only recovering the already allowed costs of manufacture, handling and development) would have a number of negative effects on the clinical research process.

Unfortunately, the positions taken in the above excerpt and in the final entry of the MNCF FAQ document serve only to limit the number of patients allowed a chance to extend, improve or even save their lives when they are unable to gain access to a drug in a clinical trial. The position in the letter appears to be that sponsors must not be allowed to make a profit, even if failing to allow a company to make a profit leaves in place one of the major economic disincentives that has caused the EAP process to fall far short of patient need. As a result, tens of thousands of patients will continue to die having been denied access to the only reasonable treatment options still available, solely because some advocates, and in our experience the FDA, do not want sponsors to be given the incentives needed to provide more and larger access programs for their investigational drugs. This position is indefensible given that current regulations and most patient advocates already acknowledge that such access is appropriate, that sponsors should be allowed to recover costs (*i.e.*, charge) for their drugs, and that the clinical trials system can be protected by implementing precisely the controls we are proposing for Tier 1. It is also important to note that several large EAPs have been conducted by sponsors without significant negative effects on the enrollment and conduct of simultaneous clinical trials. There is simply no evidence to support a concern that wider access to investigational drugs for patients who cannot gain access in clinical trials will undermine the clinical research and regulatory process.

Finally, we know from our personal experiences and those of our constituents that being denied access to investigational drugs that might help when no other options exist is most certainly not in the "interest of cancer patients" facing certain death from their disease.

Excerpt No. 9

The treatment landscape is littered with examples of treatment options that looked promising in early stages of development only to prove ineffective in Phase II or Phase III trials. Many of these treatments have not reached the public eye due to commercial confidentiality. We have seen over and over that the only way to truly show efficacy in the current technological and scientific environment is through controlled trials. This is particularly true if the benefit increment is small. In addition, from the experience with Gleevec and Eloxatin, we know that when a drug shows exceptional promise in early trials, that FDA can be counted upon to facilitate the approval process in record time.

Response

While Gleevec is sometimes cited as an example of the FDA acting quickly to approve a drug, many people died from CML after the sponsors and FDA knew they had a major advance that was going to be approved in "record" time. Unfortunately, the FDA's process still required many months to produce an application, complete review, and eventually issue approval. Some patients got Gleevec prior to approval through existing access mechanisms, but many did not.

The story of Eloxatin is actually one of the most troubling examples of FDA as a barrier to access. It is a strong example of why we need Tier 1. The FDA did not quickly approve Eloxatin as implied in the excerpt. Eloxatin was first approved in France in 1996, and became widely available around the world by 2000, but not in the U.S. It was first rejected by the FDA (with help from the ODAC) in March 2000 by an FDA that was beginning a process of making a series of mistakes that would directly and negatively affect colon cancer patients. It was available in at least 56 other countries by the time it was finally approved in the U.S., two and one-half years after its initial rejection, long after there was considerable evidence that it was a safe and effective drug.

FDA's performance with Eloxatin and their later failure with Erbitux became a major "denial of access" problem for tens of thousands of colon cancer patients. Tier 1 would have greatly alleviated those problems for the tens of thousands of patients who died without gaining access to Eloxatin, now the rapidly emerging new standard of care, and Erbitux, a drug that will instantly be accepted upon approval as the only safe and effective third line option for colon cancer patients. It is interesting to note that Eloxatin has gained rapid acceptance as both a first- and second-line therapy for colon cancer in the U.S. within a few months of approval. Perhaps that occurred because the NCI was on record months before the drug's approval stating that FOLFOX was likely the best first-line therapy available (although at that time it was not available to most Americans with colon cancer).

We counsel all who work closely with the FDA to be careful in accepting the agency's sometimes too conservative approach to decision-making and often too laudatory efforts at self-promotion. The FDA does make mistakes, and does not leap to fix them when that happens. The agency's self-promotion after its belated approval of Eloxatin was not well received by many colon cancer patients and their caregivers in August 2002, and is not a good example for supporting the statement that the FDA "can be counted upon to facilitate the approval process in record time."

The truth is that the FDA has no means of practicing emergency response. Tier 1 Initial Approval would provide the agency with a real emergency response capability for the first time in its history.

We must look forward to the hundreds of new oncology drugs in the pipeline that include monoclonal antibodies that work, patient-specific vaccines that are showing undeniable evidence of effectiveness, angiogenesis inhibitors that will soon be approved and extending lives, and the many other new therapies that are beginning and will continue to transform the face of health care.

We also must clearly acknowledge that individualized medicine based on vaccines, gene sequencing and proteomics is coming and in some respects is already here. The system we have now based on trials of standardized compounds simply won't work for evaluating patient-specific treatments. We are going to be doing a lot of adjusting to scientific progress over the next several decades, Tier 1 Initial Approval gives us a mechanism to make sure we don't leave the patients out of the progress.

Excerpt No. 10

We believe that it is here, in the existing regulatory process, that we should place our hope for better outcomes and lives saved when they can be, and extended when they cannot. As Patient Representatives/Consultants, we are counting on you to ensure that good science continues to prevail in drug development.

Response

The Abigail Alliance does not oppose good science. The entire focus of our effort is to get the fruits of scientific research faster to patients who have no other options. We do not, however, believe "the existing regulatory process" is sacrosanct. The notion that nothing in this process can be altered to open up compassionate use to a greater number of dying patients is an extreme position. It is a position with which we respectfully, but vigorously, disagree.

Conclusion

We believe the Tier 1 concept is a sound framework to better serve the needs of hundreds of thousands of Americans that are now being abandoned. Disagreements over specific details of the proposal should not stand in the way of work on access to new therapies for the terminally ill. We are encouraged that our petition and lawsuit have prompted some to apply their knowledge, passion and perspectives to help those we all are trying serve, and hope you will work with us directly to create viable solutions.

Please commence a rulemaking based on the proposal described in our Citizen Petition. It is our goal, and we believe also yours, to improve the responsiveness of our system in a timeframe that is meaningful to the tens of thousands of patients who need help now.

Sincerely,

Frank Burroughs

Frank Burroughs, President

Steve Walker

Steve Walker, Advisor on FDA and Regulatory Issues

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Expanded Access – FAQs

Marti Nelson Cancer Foundation

What good does an expanded access program do?

A well-designed expanded access program offers a treatment option to patients who frequently have no other options. In addition, it can provide information – safety, quality of life – about the drug in a 'real world' setting, and increase patient/provider knowledge and 'buzz' about the drug before it hits the market. Thus, both patients and companies can benefit from a properly designed and executed expanded access program.

When should expanded access be considered? What about drugs that are being tested in several forms of cancer?

Expanded access should be considered when a population of patients who might benefit from the treatment can be defined – for example, after Phase 2 trial results are known, or once interim Phase 3 trial results show a benefit.

A drug that shows benefit in one form of cancer may not produce a similar benefit in another cancer, which is why some level of efficacy data is important. As targeted treatments become more common, the argument could be made that any type of tumor with the appropriate molecular markers might respond to treatment with a drug. This is a good argument that should be tested in clinical trials.

Some argue that compassionate use gets in the way of clinical trials.

Exclusion criteria for expanded access can state that if a patient is eligible for the trial, he is ineligible for expanded access.

Some argue that compassionate use is a bad use of resources. In other words, they feel that in cases where developmental drugs are in short supply, surplus drug should be used for additional research. In addition, the programs are expensive especially if additional data (safety, quality of life) is gathered.

There are times, especially with large molecule drugs, where the resource supply issue is valid. Manufacturing biologics as opposed to drugs can be complex and expensive. Both time and money are required to qualify a new manufacturing plant under FDA guidelines. There are verifiable supply constraints that may greatly limit the amount of drug available to both clinical trials and expanded access programs.

At the same time, many expanded access programs when a manufacturer begins to ramp up supply of a drug prior to expected approval. In this situation, expanded access is possible.

The expense of the programs is a very real issue. On the other hand, EAPs offer an opportunity to learn tremendous amounts about the drug prior to large-scale marketing. A clear understanding of safety, side effects and quality of life issues benefits patients tremendously.

Some argue that compassionate use is actually cruel, because in most cases it's not clear that the drug will actually benefit the patient. In addition, if the drug is in short supply and a lottery is used to allocate the drug, the stress involved is very difficult for patients to handle.

Cancer is cruel. No cancer drugs are effective for all patients. Searching for treatment options is stressful. Patients have the right to make fully informed decisions about their treatment options, including the use of developmental drugs when appropriate.

Why expanded access instead of single patient compassionate use?

Individual compassionate use can be much more difficult for a company to deal with than a defined program with well-described qualification procedures. Expanded access makes an experimental drug available to people within a defined population. When supplies are limited, an expanded access program can operate via a completely objective allocation system, like a lottery. A single patient access approach is, by nature, not objective. At the same time, there are times, especially for patients with very rare cancers, when single patient compassionate use may be appropriate.

Some have suggested that drug manufacturers should be allowed to profit from selling experimental drugs prior to completing required safety and efficacy testing. Wouldn't this be a better approach than EAPs?

Unfortunately, history is full of examples where people with life-threatening illnesses are exploited for short-term profits. In fact, there have been very few dramatic advances in the treatment of cancer that have not required long patient testing, optimization, and careful assessment of safety risks.

We believe that profits are appropriate only after a rigorous assessment of both safety and efficacy has demonstrated that a new drug has value in treating the target disease and works for a reasonable proportion of the target population. In addition, experience gained with the "accelerated approval" mechanism has demonstrated that early profits don't necessarily correlate with speedier development of effective new treatments for cancer or other life-threatening diseases.

Properly designed EAPs offer a good opportunity to make promising experimental drugs available to patients who have exhausted other options without interfering with the clinical research process. In fact, EAPs have the potential to enhance the clinical research process because of the additional information they provide about use of the treatment in a real-world population.

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October 7, 2003

Dockets Management Branch
Food and Drug Administration
5630 Fishers Lane
Room 1061, HFA-305
Rockville, MD 20852

Re: Citizen Petition -- *In re* Tier 1 Initial Approval (Docket No. 2003P-0274/CP1)

Dear Sir or Madam:

Enclosed please find four copies of our submission entitled "Response to submission from Ms. Musa Mayer *et al.* regarding 'Tier 1 Initial Approval,'" which we respectfully submit for filing by your office.

Very truly yours,

David Price

David Price
Senior Vice President, Legal Affairs

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